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Calmodulin Kinases II and IV and Calcineurin Are Involved in Leukemia Inhibitory Factor–Induced Cardiac Hypertrophy in Rats

Takahiro Kato,* Motoaki Sano,* Shunichiro Miyoshi, Toshihiko Sato, Daihiko Hakuno, Hideyuki Ishida, Hiroe Kinoshita-Nakazawa, Keiichi Fukuda, Satoshi Ogawa

Abstract—We recently reported that leukemia inhibitory factor (LIF) enhances $Ca^{2+}]_i$ through an increase in L-type Ca^{2+} current ($I_{Ca,L}$) in adult cardiomyocytes. The aim of this study was to investigate whether LIF activates Ca^{2+}-dependent signaling molecules, such as calcineurin and calmodulin kinases II and IV (CaMKII and CaMKIV), and, if so, whether these Ca^{2+}-mediated signaling events contribute to LIF-mediated cardiac hypertrophy. We first confirmed that LIF increased $I_{Ca,L}$ and $[Ca^{2+}]_i$ in primary cultured rat neonatal cardiomyocytes. Calcineurin, CaMKII, and CaMKIV activities increased at 2 minutes and peaked by 1.6-, 2.2-, and 2.2-fold, respectively, at 15 minutes. Nicardipine or verapamil fully inhibited these activities. Autophosphorylation of CaMKII was also observed to parallel the timing of CaMKII activity, and this phosphorylation was blocked by nicardipine, verapamil, or EGTA. LIF treatment led to a 3-fold increase in nuclear factor of activated T cell–luciferase activity. To confirm that inositol triphosphate (IP_3)-induced Ca^{2+} release from sarcoplasmic reticulum was not involved in this process, IP_3 content and phosphorylation of phospholipase Cγ were investigated. LIF did not increase IP_3 content or phosphorylate phospholipase Cγ. KN62 (an inhibitor of CaMKII and CaMKIV) attenuated c-fos, brain natriuretic peptide, α-skeletal actin, and atrial natriuretic peptide expression. KN62 suppressed the LIF-induced increase in [^{3}H]phenylalanine uptake and cell size. Cyclosporin A and FK506 slightly attenuated brain natriuretic peptide but did not affect c-fos or atrial natriuretic peptide expression. Cyclosporin A significantly reduced the LIF-induced increase in [^{3}H]phenylalanine uptake. These findings indicated that LIF activated CaMKII, CaMKIV, and calcineurin through an increase in $I_{Ca,L}$ and $[Ca^{2+}]_i$ and that CaMKII, CaMKIV, and calcineurin are critically involved in LIF-induced cardiac hypertrophy. (***Circ Res.* 2000;87:937-945.)**

Key Words: leukemia inhibitory factor ■ calcium ■ calmodulin-dependent kinase ■ calcineurin ■ cardiac hypertrophy

Leukemia inhibitory factor (LIF), a member of the interleukin-6 family of cytokines, has a potent hypertrophic effect on cardiomyocytes. However, the underlying molecular mechanisms that couple hypertrophic signals initiated at the cell membrane receptor to the reprogramming of cardiomyocyte gene expression remain poorly understood. We and others have demonstrated that the Janus kinase and signal transducers and activators of transcription pathway, mitogen-activated protein kinase (MAPK) pathway, and phosphatidyl inositol 3 (PI3) kinase pathway were present downstream of gp130 in cardiomyocytes.[1-4] We recently reported that LIF enhanced L-type Ca^{2+} current by 42% and $[Ca^{2+}]_i$ transient by 63% in cardiomyocytes.[5] Interestingly, LIF-induced increases in L-type Ca^{2+} current and $[Ca^{2+}]_i$ transient took a unique time course, which gradually increased from 2 minutes and peaked at 15 minutes. Moreover, although the precise mechanism remains unknown, these increases were not mediated by protein kinase A (PKA) or protein kinase C (PKC) pathways.

There is a growing body of evidence to suggest that Ca^{2+} signaling plays an important role in the pathogenesis of cardiac hypertrophy and heart failure. Recently, the Ca^{2+}/calmodulin–dependent protein phosphatase calcineurin has attracted attention as a new signal transducer of hypertrophic stimuli in vitro and in vivo. Calcineurin dephosphorylates the nuclear factor of activated T cells (NFAT)-3 transcription factor, which is then translocated into the nucleus. Recently, Molkentin et al[6] reported that NFAT-3, GATA-4, and calcineurin synergistically activate a marker gene of cardiac hypertrophy. In cultured cardiomyocytes, cyclosporin A (CsA), an inhibitor of calcineurin activity, inhibited angiotensin II–induced and phenylephrine-induced cardiac hypertrophy. Cardiac overexpression of the constitutively active form of calcineurin and NFAT-3 caused marked hypertrophy

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From the Cardiopulmonary Division, Department of Internal Medicine (T.K., M.S., S.M., T.S., D.H., K.F., S.O.), Keio University, Tokyo, Japan, and Department of Physiology (H.I., H.K.-N.), Tokai University, Kanagawa, Japan.

*Both authors contributed equally to this study.

Correspondence to Keiichi Fukuda, MD, PhD, Cardiopulmonary Division, Department of Internal Medicine, Keio University School of Medicine, 35 Shinanomachi, Shinjuku-ku, Tokyo 160-8582, Japan. E-mail kfukuda@mc.med.keio.ac.jp

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